

# Open Public Consultation on the revision of EU rules on medicines for children and rare diseases

Fields marked with \* are mandatory.

## Introduction

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The EU rules on medicines for rare diseases and medicines for children were adopted in 2000 and 2006, respectively. The rules were designed to improve the treatment options available to 30 million European patients affected by one of over 6000 rare diseases, as well as for 100 million European children affected by paediatric diseases. At the time, there were limited or no medicinal products available for treatment of both groups.

A recent evaluation of the rules showed that they have stimulated research and development of medicines to treat rare diseases and other conditions affecting children. However, the evaluation also revealed shortcomings in the current system. The rules have not been effective for stimulating the development of medicines in areas of unmet needs (e.g. 95% of rare diseases still have no treatment option), and they have not ensured that the medicines are accessible to all European patients across all Member States.

The rules provide incentives and rewards, and their design can influence business decisions on research and development for new medicines, as well as whether such investment can be focused in areas of the greatest need for patients. In addition, the system of incentives can impact market competition and indirectly influence the availability of and access to those medicines by EU patients.

## About you

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- Public authority
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- Other

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\* Organisation name

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Medicines for Europe

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## Questionnaire on the revision of EU rules for medicines for rare diseases and children

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**Q1: The main problems identified in the evaluation of the legislation for medicines for rare diseases and for children were the following:**

- **Insufficient development in areas of the greatest needs for patients.**
- **Unequal availability, delayed access, and often unaffordable treatments for patients in the EU Member States.**
- **Inadequate measures to adopt scientific and technological developments in the areas of paediatric and rare diseases.**

**In your opinion, are there any other barriers to the development of treatments for rare diseases and children?**

*2000 character(s) maximum*

Due to the peculiar off-patent market dynamics for orphan products, also generic & biosimilar companies should be incentivised to develop follow-on orphans. Currently, there are R&D, regulatory & market access barriers hindering investments in follow-on orphan medicines:

- lack of regulatory framework allowing single development of follow-on orphans for multiple jurisdictions, need to repeat studies with local reference products, lack of one development program/one data package (comparable to international harmonisation of originators orphan development, where single development is possible), with subsequent difficulties in patient recruitment, lack of tailored clinical requirements (eg, waiver of clinical comparability studies, more flexibility in clinical study design, support in procuring comparator products, etc.). Single development would solve the difficulty to obtain a comparator product for studies, remove barriers to patient recruitment for CT, etc.
- limited market (ie. small population to be treated)
- lack of regulatory or scientific advice fee waivers
- lack of accelerated market approval for follow-on orphans
- lack of reduced timelines for P&R decisions, in line with the purposes of Bolar
- lack of P&R tailoring.

As to off-patent incentives for paediatric medicines, PUMA alone has shown to be insufficient to overcome existing barriers & incentivise development of off-patent paediatric products. There is need to enhance the incentives available (both pull & push incentives should be considered) in the off-patent paediatric sector to recognise investments in trials & tackle different requirements country by country. New measures should be adopted to stimulate investments, as detailed below. For more off-patent paediatric development, we need to link approval procedures, innovation frameworks & reimbursement processes to create an ecosystem delivering better health to patients, solutions for healthcare systems & fair returns on R&D investments

**Q2: In your opinion, and based on your experience, what has been the additional impact of COVID-19 on the main problems identified through the evaluation? Is there a 'lesson to be learned' from the pandemic that the EU could apply in relation to medicines for rare diseases and children?**

*2000 character(s) maximum*



The Covid-19 emergency has shown the vital importance of a strong generic and biosimilar industry in Europe. 70 to 90% of the medicines used in intensive care units to treat Covid-19 patients were off-patent. Indeed, off-patent medicines (generic, biosimilar and value added) are the backbone of public health by contributing massively in delivering equitable access to medicines as well as to make healthcare systems sustainable.

Other barriers encountered were:

- Patient recruitment in paediatric trials was a big challenge
- Access to comparator innovator product for trials (due to many countries restricting product to use for treatment purpose only rather than for trials)
- Delay in IMP manufacturing due to Covid-related delays from raw material and equipment manufacturers
- Challenges in approaching clinical experts due to their pre-occupancy with Covid

It is key to tackle all the barriers that still today block generic and biosimilar entry at patent expiry. The well-functioning of the orphan and paediatric medicines sectors, including multiple sources of medicines upon expiry of exclusivities, are of utmost importance for the sustainability of patient health and healthcare systems. Ensuring that the right incentives for the off-patent sector are included in the revised rules on orphan and paediatric is pivotal, for both generic and biosimilar medicines, but also in relation to the need for a specific framework for value added medicines in the EU legislation, with more proportionate incentives & rewards for the effort invested in order to address market failures related to repurposed products and continuous innovation (eg. off-label prescribing). While off-label prescribing is not recommended in normal circumstances, if it is used in exceptional circumstances (eg. the Covid-19 emergency), studies should be conducted of such off-label use to assess the actual results.

**Q3: In your opinion, how adequate are the approaches listed below for better addressing the needs of rare disease patients?**

*at most 4 answered row(s)*

	Very adequate	Moderately adequate	Not at all adequate
When considering whether a particular medicine is eligible for support, the rarity of the disease – the total number of cases of a disease at a specific time, currently less than 5 in 10 000 people – forms the main element of the EU rules on medicines for patients suffering from rare diseases.	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>

<p>Some diseases occur frequently, but last for a relatively short period of time (for example, some rare cancers). These are covered by the EU rules on medicines for rare diseases and the principle of rarity. However, because many patients acquire such diseases during a specified, limited period of time, those diseases should <u>not</u> be considered as rare in the EU anymore.</p>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
<p>Amongst all medicines for rare diseases which become available to the EU patients, only those bringing a clear benefit to patients should be rewarded. Clear rules should apply to decide if one medicine brings a clear benefit to patients when compared to any other available treatment in the EU for a specific rare disease.</p>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
<p>Additional incentives and rewards should exist for medicines that have the potential to address the unmet needs of patients with rare diseases, for example in areas where no treatments exist.</p>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

Other (please suggest any other criteria/approaches you think might be relevant).

*2000 character(s) maximum*

In relation to the second case above (rare diseases for short times), as long as they meet the existing criteria to qualify as rare diseases, they should fall under that category.

As far as incentives are concerned, Medicines for Europe supports the incentive system, however, a holistic approach should be taken, ie. investments should be incentivised but generic and biosimilar's market launch should not be delayed after the expiry of the protections for the relevant reference product.

In relation to additional incentives, while a discussion on alternative incentives is coherent with the objectives of this review, Medicines for Europe opposes novel/additional incentives, particularly via transferrable exclusivity vouchers, as they would extend monopolies on more profitable products, dramatically increase costs for healthcare budgets, increase legal uncertainty incl. on market formation dates & unduly delay access to generics/biosimilars. It is worth noticing that no jurisdiction worldwide has any transferable exclusivities – the US transferable vouchers relate to priority reviews only.

We also oppose a strategic use in combination of the two incentives – orphan incentives (Market Exclusivity, regulatory support, etc.) and SPC extension, as it does not reflect the intention of the legislator.

**Q4: What factors are important to take into consideration when deciding if one medicine for a rare disease brings more benefits compared with other available treatments?**

*2000 character(s) maximum*

It is recommended to adopt a multi-stakeholder approach in establishing benefits. Therefore the involvement of all relevant stakeholders is essential. Very clear rules are necessary to avoid any potential abuses or misuses, and predictability for follow-on developers is essential for the well-functioning of the system.

**Q5: What do you consider to be an unmet therapeutic need of rare disease patients and children?**

- Authorised medicines for a particular rare disease or a disease affecting children are not available, and no other medical treatments are available (e.g. surgery).
- Treatments are already available, but their efficacy and/or safety is not optimal. For example, it addresses only symptoms.
- Treatments are available, but impose an elevated burden for patients. For example, frequent visits to the hospital to have the medicine administered.
- Treatments are available, but not adapted to all subpopulations. For example, no adapted doses and/or formulations, like syrups or drops exist for children.

Other (please specify).

*2000 character(s) maximum*

The criteria are set up exclusively from the perspective of / applicability to New Entities. The EU shall not ignore the opportunity to encourage off-patent medicines innovation, which generally speaking is much more affordable.

This approach can take advantage of pre-clinical data and clinical insights from existing medicines and can help de-risk R&D that addresses public health priorities and reduce the investment needed, compared to traditional innovation model.

Medicines for Europe's recommendation is to better reflect "unmet medical need"/ possible benefit coming from innovation in well-known molecules that cannot be assessed based on the same criteria as for NCEs (eg. drug repurposing or reformulation).

Repurposing is not the only opportunity for off-patent innovation in unmet needs. There are also reformulations and combinations that can be used to address issues such as AMR or tackling the poor management of chronic diseases. Reformulation is often important in delivery of medicines for children. Patient preferences and unmet needs should be considered and accounted for in regulatory and reimbursement decisions across the lifecycle of the medicine, including also innovation on well-established medicines. Ideally, value evidence requirements and evaluation should be streamlined in an early scientific and HTA/payer dialogue. Unmet therapeutic need should be defined with healthcare stakeholders: regulators, patients, healthcare professionals and payers.

The Return-on-investment (ROI) criteria may be elaborated further with clear guidance on the indications and scenarios that fit these criteria and the models to demonstrate poor ROI if the product is not granted ODD.

Consideration may be made to those indication subsets where there is a clear unmet need, when the main indication is beyond the orphan threshold of 5/10k and below 10/10K.

As to the last case described above, the patent system allows protection.

**Q6: Which of the following measures, in your view, would be most effective for boosting the development of medicines addressing unmet therapeutic need of patients suffering from a rare disease and/or for children? (1 being the least effective, 10 being the most effective)**

*at most 4 answered row(s)*

	1	2	3	4	5	6	7	8	9	10
Assistance with Research & Development (R&D), where medicines under the development can benefit from national and/or EU funding	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

Additional scientific support for the development of medicines from the European Medicines Agency	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
Assistance with authorisation procedures, such as priority review of the application from the European Medicines Agency and/or expedited approval from the European Commission	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Additional post-authorisation incentives that complement or replace the current incentives and rewards	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Do you have other suggestions that would allow the EU to boost the development of specific medicinal products?

*2000 character(s) maximum*

Some proposals above are already in the legislation. Priority reviews are welcome for products addressing real unmet needs.

As to post-authorisation incentives, while alternative incentives are coherent with the current review, we oppose novel/additional incentives, particularly via transferrable exclusivity vouchers, as they would extend monopolies on more profitable products, dramatically increase costs for HC budgets, increase legal uncertainty incl. on market formation dates & unduly delay access to generics/biosimilars.

As to the off-patent sector, as stressed in the pharma strategy communication, there is need to “stimulate innovation in particular in areas of unmet needs”, incl. off-patent paediatric developments, where there is “absence of commercial interest”. As proposed for novel antimicrobials, the reform should include pull incentives based on new P&R models to incentivise development of off-patent paediatric medicines, but also free pre-submission scientific advice (as for orphans) & clear framework for repurposed off-patent products for totally new indications for children only.

To stimulate faster competition in follow-on orphans (ie. on day-1 of exclusivity expiry) & investments in off-patent paediatrics, the reform should:

- tackle barriers to development by tailoring clinical requirements for biosimilars based on science & allow single development for multiple jurisdictions (comparable to paediatric & orphan development of originator products), as well as the regulatory incentives for originator orphans, ie. accelerated market approval, waived regulatory/scientific advice fees, etc.
- facilitate access to reference product for CTs
- remove barriers to day-1 launch after protections expire: ban patent linkage, enlarge the Bolar exemption & introduce uptake measures to stimulate competition
- reduce timelines and obstructions to P&R decisions in line with Bolar
- P&R uptake measures to encourage investments in follow-on orphan development.

Do you see any drawbacks with the approaches above? Please describe.

*2000 character(s) maximum*

So far, the focus of the incentives has been on new medicines only. However, off-patent medicines, which play a vital role, require certain incentives to be able to compete and generate a dynamic market environment for the benefit of patients, healthcare budgets and the whole system. The following priorities are essential:

- tackle barriers to development by tailoring clinical requirements for biosimilars based on science & allow single development for multiple jurisdictions (comparable to international harmonisation of paediatric & orphan development of originator products), as well as the regulatory incentives for originator orphans, ie. accelerated market approval, waived regulatory/scientific advice fees, etc.
- facilitate access to reference product for clinical trials
- remove barriers to day-1 launch after protections expire by banning patent linkage, harmonising/enlarging the Bolar exemption & introducing uptake measures to stimulate competition
- reduce timelines and obstructions to P&R decisions in line with Bolar
- P&R uptake measures to encourage investments in follow-on orphan development.

**Q7: Which of the following options, in your view, could help all EU patients (irrespective of where they live within the EU) to provide them with better access to medicines and treatments for rare diseases or children?**

- Greater availability of alternative treatment options. For instance, by allowing a generic or biosimilar product to enter the market faster.
- Allowing companies that lose commercial interest in a rare disease or children medicine product to transfer its product to another company, encouraging further development and market continuity.
- For companies to benefit from full support and incentives, products need to be placed timely on the market within all Member States in need as soon as they received a marketing authorisation.

Other (please suggest any other solution you think might be relevant).

*2000 character(s) maximum*

Stimulating investments in follow on orphan & off-patent orphan & paediatric sectors is fundamental to improve equitable access.

We recommend these regulatory measures to incentivise competition in the orphan medicines field:

- When creating incentives for innovation, it is essential to consider follow-on products that increase patient access to therapies, most of which become standards of care after exclusivities expire
- Waiving regulatory/scientific advice fees & accelerated market approval for follow-on orphans
- Tailoring of clinical requirements for follow-on orphans (esp. biosimilars)
- Single development for follow-on orphans (one data package for multiple jurisdictions)
- Remove barriers to day-1 launch after IP expire by banning patent linkage, harmonising Bolar & introducing pro-competitive uptake measures
- Reduce timelines & obstructions to P&R decisions in line with Bolar
- Fit-for-purpose P&R rules to ensure sufficient return-on-investment

We recommend the following measures to stimulate investments in off-patent paediatric medicines:

- Single development to allow one development process for multiple jurisdictions in the paediatric field
- Waiving regulatory fees: as for follow-on orphan products, regulatory fees in the paediatric field are extremely costly. Their reduction would be significantly beneficial to encouraging competition
- R&D Subsidies for off-patent paediatric research, due to limited profitability of paediatric off-patent markets
- P&R tailoring: as stressed above, as proposed for novel antimicrobials, the reform should include pull incentives based on new P&R models to incentivise development of off-patent paediatric medicines. This would help address market failures related to repurposed products & continuous innovation (eg. off-label prescribing)

The possibility to transfer its product to another company for loss of commercial interest would work only as long as not used strategically for evergreening purposes.

**Q8: Most of the medicines for rare diseases are innovative medicines. However, in some cases, an older, well-known medicine for a common disease can be repurposed (i.e., using existing licensed medicines for new medical uses) to treat a rare disease. In your view, what would be the appropriate way to award innovative medicines in cases where other treatments are available:**

- Both new, innovative medicines and well-known medicines repurposed to treat a rare disease should receive the same reward
- New, innovative medicines to treat a rare disease should receive an enhanced reward
- Do not know/cannot answer

**Q9: Despite the presence of a dedicated procedure (the Paediatric Use Marketing Authorisation, PUMA) in the Paediatric Regulation, many older medicines that are currently used to treat children have only been studied for use within adult populations, and therefore lack the appropriate dosage or formulation suitable for use in younger patients. However, the development of medicines that have been adapted for use in children could also result in a product being more expensive than its adult-focused counterpart. In your view:**

Should the development of appropriate dosage or formulation suitable for children of such older medicines be stimulated even if their price will be higher than that of the available alternatives?

- Yes
- No
- Do not know/cannot answer

Please explain your answer.

*2000 character(s) maximum*

Since in the off-patent paediatric sector there is no possibility to obtain an exclusivity (such as a 6-month SPC for patented products), as stressed in the pharma strategy communication, there is need to “stimulate innovation in particular in areas of unmet needs”, incl. off-patent paediatric developments, where there is “absence of commercial interest”. As proposed for novel antimicrobials, the reform should include pull incentives based on new P&R models to incentivise development of off-patent paediatric medicines. This would help address market failures related to repurposed products and continuous innovation (eg. off-label prescribing).

It is essential that a clear link be provided for in the legislation between PUMA products and new P&R models. In case of PUMA for a given indication, measures should be introduced to avoid off-label use. It is crucial that national authorities explore ways to prioritise use of such approved medicines over off-label use, in order to avoid that the PUMA incentive would not effectively produce the intended benefits. In addition, incentivisation for on-patent PUMA should also be foreseen, for instance encouraging mechanisms of cooperation between developers and patent holders via voluntary licensing agreements.

How would you suggest stimulating further development of appropriate dosage or formulation suitable for children of such older medicines?

*2000 character(s) maximum*



PUMA has been used only rarely. PUMA alone is insufficient to incentivise off-patent paediatric products. There is need to enhance incentives available in the off-patent paediatric sector.

New measures should be adopted to stimulate investments:

- Single development to allow one devt process for multiple jurisdictions in the paediatric field
- Waiving regulatory fees: as for follow-on orphan products, regulatory fees in the paediatric field are extremely costly. Their reduction would significantly stimulate competition
- R&D Subsidies for off-patent paediatric research, due to limited profitability of paediatric off-patent markets
- P&R tailoring: current P&R rules are not fit-for-purpose & do not deliver sufficient return-on-investment for paediatric development if other generic/biosimilar alternatives are available. As proposed for novel antimicrobials, the reform should include pull incentives based on new P&R models to incentivise development of off-patent paediatric medicines.

In case of repurposing, it is crucial that national authorities explore ways to prioritise use of such approved medicines over off-label use.

There is confusion in EU markets regarding fair valuation of off-patent innovation. Value assessment process are heterogeneous across EU Member States & Value Added Medicines (including paediatrics) are often categorised as generic medicines, since innovation is on off-patent molecules, with no framework in place to recognise their additional value in a proportionate way. In other cases, manufacturers face requests for evidence in HTA processes designed for originator medicines & therefore demand disproportionate evidence generation. Hence, P&R rules should be shaped to adequately assess continuous innovation & adjusted to the specificity: a tailored process should be established, since the current pathways for generics (eg. internal price referencing, mandatory discounts) or innovative medicines are not appropriate for VAMs.

## How can it be ensured that such developed products are reasonably profitable for companies and also reach patients?

*2000 character(s) maximum*

On PUMA, there is a recognised market failure. Indeed, as stressed in the pharma strategy communication, there is need to “stimulate innovation in particular in areas of unmet needs”, incl. off-patent paediatric developments, where there is “absence of commercial interest”. As is proposed for novel antimicrobials, the reform should include pull incentives based on new P&R models to incentivise development of off-patent paediatric medicines, but also free pre-submission scientific advice (as for orphans) & a clear framework for repurposed off-patent products for totally new indications for children only.

It is essential that a clear link be provided for in the legislation between PUMA products and new P&R models. In case of PUMA for a given indication, measures should be introduced to avoid off-label use. It is crucial that national authorities explore ways to prioritise use of such approved medicines over off-label use, in order to avoid that the PUMA incentive would not effectively produce the intended benefits. In addition, incentivisation for on-patent PUMA should also be foreseen, for instance encouraging mechanisms of cooperation between developers and patent holders via voluntary licensing agreements.

Often in paediatric developments it should also be considered that the same formulation as for the adult population may not be a best fit for children and, therefore, manufacturers should be encouraged and incentivised to reformulate medicines for paediatric use as well. As stressed above, P&R rules should be shaped to adequately assess continuous innovation and adjusted to the specificity: a tailored process should be established, as the current pathways for generic medicines (eg. internal price referencing, mandatory discounts) or innovative medicines are not appropriate for VAMs.

## Contact

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